

PATENT
09/994,440
Docket 091/010c

REMARKS

This paper is responsive to the Office Action dated January 16, 2004, which is the first action on the merits of the application.

Claims 1-15 were previously pending, and stand variously rejected. Upon entry of this paper, certain claims are amended. No claims have been cancelled or added.

Further consideration and allowance of the application is respectfully requested.

Amendments:

Entry of the amendments to the specification does not introduce new matter into the disclosure. Additional wording present in the paragraph being replaced on page 16 of the specification is taken from USSN 60/213,739, page 21, lines 10-13. This application claims the priority benefit of USSN 60/213,739, and incorporates it by reference on page 1, lines 13-18 of the application as filed.

Entry of the claim amendments does not introduce new matter into the disclosure. Support for the use of extracellular matrix in the feeder-free culture system of the invention can be found in several places in the disclosure, such as page 15, lines 15-27, Example 2 (page 40 ff.), and Figure 3.

Double Patenting

Certain claims in this application stand provisionally rejected for double patenting, with respect to certain claims of pending applications USSN 10/330,873; 10/325,094; 09/859,291; and 10/087,473.

The prosecution of the present application is further advanced than USSN 10/330,873; and 10/325,094, for which applicant has not yet received a first Office Action on the merits. In the normal course of things, applicant expects the invention claimed in the present application to be patented before the claims in USSN 10/330,873; and 10/325,094.

With respect to USSN 09/859,291; and 10/087,473, applicant undertakes to address this issue appropriately upon determination that the claims in the present application and in USSN 09/859,291; and 10/087,473 are otherwise patentable.

PATENT
09/994,440
Docket 091/010c

Rejections under 35 USC § 112 ¶ 1:

Claims 1-15 stand rejected under the enablement requirement of § 112 ¶ 1. The Office Action indicates that the specification is enabling for methods of making differentiated cells from cultured blastocyst-derived pPS cells on an extracellular matrix in a fibroblast conditioned medium, but not in other media. The Office Action states that the [specification] contemplates using nutrient medium that contains exogenously added factors, but there are no working examples to show that such medium would be sufficient to maintain hES cells in an undifferentiated state.

Applicant is grateful for acknowledgement that the specification is enabled to the extent indicated in the Office Action.

Applicant respectfully disagrees that the claims need to be limited in the manner suggested. The following arguments parallel those made in copending application USSN 09/859,291, in which a similar issue was raised.

By making this rejection, the Office seeks to limit applicant's coverage to conditions that were exemplified in the working examples. But the details of growth conditions selected for the working examples, such as the medium used, are not critical features of the new feeder-free culture method described and enabled by the application.

Federal Circuit case law clearly establishes that a patent applicant is not required to limit coverage to the working examples. Broader coverage is available under § 112 ¶ 1, providing there is no prior art that encroaches on the claimed scope outside the working examples.

For example, *In re Peters*, 221 USPQ 952 (Fed. Cir. 1983) and *In re Rasmussen*, 211 USPQ 323 (Cust. & Pat. App. 1981) both held that applicants are entitled to eliminate a non-critical limitation from the claims in a reexamination application, *even though the Patent Office demonstrated in each case that the specification had no working example that omitted the limitation at issue*. Similarly, the PTO was found to err when it rejected a claim to an analog of human γ -interferon having only one particular alteration, when the specification taught how to make an analog that had the same alteration in combination with another alteration. *In re Alton*, 37 USPQ2d 1578 (Fed. Cir. 1996).

The specification of the present application clearly indicates that the aspects of the culture system referred to in the current Office Action are not considered critical to the invention. In the section of the Detailed Description dealing with the culture of pPS cells in the absence of feeders, key elements of the medium are indicated on page 16, lines 8-11.

PATENT
09/994,440
Docket 091/010c

pPS cells plated in the absence of fresh feeder cells benefit from being cultured in a nutrient medium. The medium will generally contain the usual components to enhance cell survival, including isotonic buffer, essential minerals, and either serum or a serum replacement of some kind.

The description goes on to highlight the use of conditioned medium as a possible nutrient medium to be used in the feeder-free environment. At the time the application was filed, conditioned medium was a preferred embodiment of the invention. For this reason, the manufacture and use of conditioned medium was elaborated, in a spirit of full disclosure and compliance with the best mode requirements of § 112 ¶ 1.

In addition, some of the cell lines used to condition the medium represent an embodiment of the invention for which coverage is being sought in a related application. Such cell lines include any human cell including but not limited to those obtained by differentiating hES cells that have appropriate characteristics to condition medium, which can be identified according to the testing procedure described on page 18, line 23 to page 19, line 10. Suitable cells may have features that are characteristic of fibroblasts, or other cell types such as *mesenchymal cells* (page 17, lines 22-25).

However, none of these aspects of the culture environment exemplified in the specification are meant to limit the feeder-free system of the invention (as embodied in the present claims) to the particular culture conditions used in the working examples. By way of this amendment, wording has been incorporated into the specification from priority application USSN 60/213,739. This wording confirms what would already be apparent to the skilled reader — that the feeder-free system can be practiced not only by conditioning the nutrient medium by preculturing with feeder cells, but by synthetically assembling an effective nutrient medium by adding the growth factors directly to fresh medium.

Now that applicant has demonstrated that human ES cells can be established and maintained in a feeder-free environment, working alternatives can be identified and used by the skilled reader. By employing the culture test system and the marker assessment protocol provided in the specification (e.g., Examples 1-3), synthetically assembled media can be used and assessed to identify effective combinations of culture environment components. Now that applicant has disclosed the feeder-free system to the art by the filing and publication of this patent application, it would be unfair to limit applicant to culture conditions exemplified in the working examples.

Besides the results shown in the working examples of this patent disclosure, the scientists at Geron have also demonstrated that human ES cells readily grow in fresh medium with added growth

PATENT
09/994,440
Docket 091/010c

factors. X-VIVO™ 10 and QBSF™-60 (two commercially available formulations) are suitable as the base nutrient medium. Basic FGF (used with or without Flt-3 ligand or stem cell factor) are added to the medium to replace the signaling provided by feeder cells in feeder-supported culture, or by conditioned medium. The synthetic medium supports expansion of human ES cells in an undifferentiated form for prolonged culture, as demonstrated by retention of markers characteristic of the undifferentiated phenotype, and by sustained ability to differentiate into tissue types representing all three germ layers.

To expedite prosecution of the application, the claims have now been amended to indicate that the culture environment contains an extracellular matrix. Applicant respectfully submits that the base claim need not also recite the use of conditioned medium, since this is a preferred embodiment, and not a critical limitation.

Rejections under 35 USC § 112 ¶ 2:

Claim 2 stands rejected as referring to a medium component being withdrawn from the culture environment. While not agreeing with the points made in the Office Action, applicant has amended this claim in a way which is believed to obviate this rejection.

Request for Interview

Applicant respectfully requests that all outstanding rejections be reconsidered and withdrawn. The application is believed to be in condition for allowance, and a prompt Notice of Allowance is requested. In the event that the Examiner determines that there are other matters to be addressed, applicant hereby requests an interview by telephone.

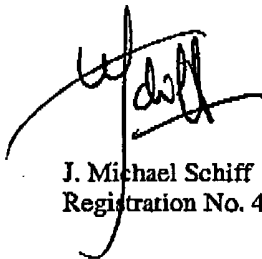
PATENT
09/994,440
Docket 091/010c

Fees Due

The accompanying papers authorize the Commissioner to charge applicant's deposit account for the extension fee. No fee is required with respect to the amendments to the claims.

Should the Patent Office determine that a further extension of time or any other relief is required for further consideration of this application, applicant hereby petitions for such relief, and authorizes the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139, referencing the docket number indicated above.

Respectfully submitted,



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Last page of this transmission